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Director
Registration Division (TS767C)
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Crystal Mall No. 2, Room 716D
Arlington, Virginia 22202

Attention: Mr. Robert J. Taylor
Product Manager (25)

Subject: Roundup® Herbicide
EPA Reg. No. 524-308
Additional Information
Relating to Chronic Mouse
Study, BD-77-420

Dear Sir:

On July 29, 1983, Monsanto submitted to the Agency an eight volume report entitled "A Chronic Feeding Study of Glyphosate in Mice," BD-77-420. The accession numbers 251007-251014 were assigned to this submission.

On March 20, 1984 we provided the Agency historical data for the incidence of renal tubular adenomas in control groups of comparable studies conducted at Bio/dynamics, Inc. In addition, historical control data for this lesion were also provided from two other major contract laboratories.

The purpose of this letter is to offer additional comments and information which we believe further supports our conclusion that the occurrence of this lesion in the glyphosate mouse study is unrelated to treatment.

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1. An important criterion in the differentiation of treatment-related effects from those occurring simply by chance is whether the alleged adverse effect is observed in both male and female animals. While there are cases in which sex-specific, treatment related changes can be identified, these infrequent instances are generally attributable to sex-specific differences in metabolism, sex-specific target organs, i.e. testes or ovaries or hormonal status. Certain spontaneous lesions, however, have been found to be sex-specific. A notable example is the increased incidence of various kidney lesions in the aged, male rodent as compared to females of the same species, age and strain.[1] Among the kidney lesions following this pattern are renal tubular adenomas. Historically, this lesion is observed only in male animals[2-5]. Control animal data from several laboratories indicate an historical control incidence in females of zero.

   In the glyphosate mouse study, this lesion was observed at low frequency only in male animals. Additionally, this same lesion was observed at a low frequency in the chronic rat study with glyphosate, in a clearly non-treatment related fashion, again in males only. Metabolism and tissue distribution studies have demonstrated that glyphosate is not metabolized differently (it is not metabolized at all) and its tissue distribution and excretion profile do not vary according to sex. Thus in both the rat and mouse, the presence of renal tubular adenomas follows the sex-specific pattern of the historical control lesion. There is no data supporting the hypothesis that glyphosate may produce a sex-specific response. In fact, as stated, there is evidence to the contrary. Thus, we believe there is strong evidence that the renal tubular adenomas observed in the mouse study are not related to glyphosate administration.

2. The renal tubular adenomas in the mouse study were observed only in animals sacrificed at the termination of the study. This supports the hypothesis that the lesion was an age related phenomenon rather than a glyphosate-related effect. If the tumors were a result of glyphosate administration, a reduction in the time-to-tumor may have been expected, particularly at the extreme dosage level (30,000 ppm or 3% of the diet) utilized in the study. This was not observed and again provides evidence that the effect was not treatment related.

3. Only benign tumors were observed in the glyphosate mouse study and the specific lesions were morphologically similar to those observed in control animals in other studies. No pre-neoplastic lesions or further progression to carcinoma were evident. Had this been a glyphosate related response, each of these effects may have been expected. They were not observed, however, which is consistent with historical control patterns of spontaneous lesions.

4. A two-year chronic toxicity/oncogenicity study in CD-1 mice (the same strain used in the glyphosate study) has been conducted with N-nitrosoglyphosate. N-nitrosoglyphosate (NNG) is the nitrosamine derivative and close structural congener of glyphosate. N-nitrosoglyphosate is excreted unmetabolized almost completely via the kidneys (identical to glyphosate) and thus might be expected to produce similar effects in that organ. No renal tubular adenomas were observed in this study in males or females. This is further evidence that the incidence of this lesion in the glyphosate mouse study is unrelated to glyphosate administration.

5. Glyphosate has been tested in a broad range of mutagenicity assays designed to assess point mutations, DNA damage or chromosomal effects in mammalian and bacterial cell systems, both in vivo and in vitro. Glyphosate was found to be non-mutagenic in all of these assays, even when tested up to the limit of solubility in vitro or to the maximum amount which could safely be injected into an animal in vivo. If one acknowledges that mutagenicity data is an indication whether or not a substance may have oncogenic potential and is useful in the evaluation of oncogenic hazards[6], this provides significant evidence that glyphosate is not likely to be oncogenic.

6. Statistical analysis of histopathology data is a tool used in the evaluation of the possible treatment relationship of an observed effect. However, the statistical comparison of these multiple endpoints, i.e. multiple lesions at multiple tissue sites, may produce an unacceptable high overall "false-positive" rate. A "false-positive" is the identification of a particular finding as statistically different from control when in actuality no difference exists or has occurred simply due to chance. For example, if 20 types of lesions were evaluated at a probability level of 0.05, the number expected to be positive by chance would not be one in 20, but rather the probability would be 64 in 100[7], an unacceptably high value. Thus, the data in the chronic mouse study was analyzed at the 0.01 probability level. The results of this evaluation indicated that the incidence of renal tubular adenomas in the high-dose males was not statistically different from controls, nor was there a statistically significant positive trend. Therefore, this is further evidence that the lesion is not treatment-related.

In summary, the lesion in question (renal tubular adenomas) has been shown to occur in the glyphosate chronic studies in a manner consistent with, and in several instances identical to, historical control patterns of the lesion. In addition, an oncogenicity test with a close structural congener of glyphosate conducted in the same strain of mice used in the glyphosate study demonstrated no renal tubular adenoma formation. All these factors are consistent with the fact that glyphosate has no demonstrable mutagenic potential and would not be expected to be oncogenic. It seems clear that the weight of evidence supports the conclusion that the low incidence of renal tubular adenomas observed in males at the highest dosage level in the glyphosate mouse study is unrelated to glyphosate administration.

This conclusion has been reached not only by Monsanto scientists, and those at Biodynamics laboratory, but by regulatory agencies worldwide. We hope this additional information resolves any concern you may have relative to this issue. We would be pleased to meet with HED Scientists to discuss these issues further if you wish.

Sincerely,

F. S. Serdy Corr. L.

Frank S. Serdy
Manager, Federal and State
Registration Affairs

/as

1. J. E. Gray, CRC Crit. Rev. Tox. 5, 115-144 (1977)

2. J. M. Faccini, E. Irisarri, A. M. Monro, Toxicology 21 279 (1981)

3. F. Homburger, A. B. Russfield, etal. Journal of the National Cancer Institute 55, 37 (1975)

4. Attachments to March 20, 1984 letter to EPA

5. 49 FR 45852, November 21, 1984

6. O. E. Paynter, Oncogenic potential: Guidance for analysis and evaluation of long term rodent studies (1984)

7. C. S. Weil, Am. Ind. Hyg. Assoc. J. 45, 663-670 (1984)